

Diagnostic and prognostic values of the QRS-T angle in patients with suspected acute decompensated heart failure

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Abstract

Aims The aim of this study was to investigate the diagnostic and prognostic utility of the QRS-T angle, an electrocardiogram (ECG) marker quantifying depolarization–repolarization heterogeneity, in patients with suspected acute decompensated heart failure (ADHF).

Methods and results We prospectively enrolled unselected patients presenting to the emergency department with symptoms suggestive of ADHF. The QRS-T angle was automatically derived from a standard 12-lead ECG recorded at presentation. The primary diagnostic endpoint was a final adjudicated diagnosis of ADHF. The primary prognostic endpoint was all-cause mortality during 2 years of follow-up. Among the 1915 patients enrolled, those with higher QRS-T angles were older, were more commonly male, and had a higher rate of co-morbidities such as arterial hypertension, coronary artery disease, or chronic kidney disease. ADHF was the final adjudicated diagnosis in 1140 (60%) patients. The QRS-T angle in patients with ADHF was significantly larger than in patients with non-cardiac causes of dyspnoea {median 110° [inter-quartile range (IQR) 46–156°] vs. median 33° [IQR 15–57°], $P < 0.001$ }. The diagnostic accuracy of the QRS-T angle as quantified by the area under the receiver operating characteristic curve (AUC) was 0.75 [95% confidence interval (CI) 0.73–0.77, $P < 0.001$], which was inferior to N-terminal pro-B-type natriuretic peptide (AUC 0.93, 95% CI 0.92–0.94, $P < 0.001$), but similar to that of high-sensitivity troponin T (AUC 0.78, 95% CI 0.76–0.80, $P = 0.09$). The AUC of the QRS-T angle for discrimination between ADHF and non-cardiac dyspnoea remained similarly high in subgroups of patients known to be diagnostically challenging, including patients older than 75 years [0.71 (95% CI 0.67–0.74)], renal failure [0.79 (95% CI 0.71–0.87)], and atrial fibrillation at presentation [0.68 (95% CI 0.60–0.76)]. Mortality rates according to QRS-T angle tertiles were 4%, 6%, and 10% after 30 days ($P < 0.001$) and 24%, 31%, and 43% after 2 years ($P < 0.001$). After adjustment for clinical, laboratory, and ECG parameters, the QRS-T angle remained an independent predictor for 2 year mortality with a 4% increase in mortality for every 20° increase in QRS-T angle ($P = 0.02$).

Conclusions The QRS-T angle is a readily available and inexpensive marker that can assist in the discrimination between ADHF and non-cardiac causes of acute dyspnoea and may aid in the risk stratification of these patients.

Keywords Acute heart failure; Heart failure; Acute dyspnoea; QRS-T angle; ECG

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Introduction

Acute decompensated heart failure (ADHF) is the most common reason for hospitalizations in the elderly and is a major cause of morbidity and mortality in the western society.¹ The majority of patients initially present to the emergency department (ED) with the chief complaint of acute dyspnoea. Given the broad differential diagnosis of this common symptom—~7% of all non-traumatic ED admissions present with respiratory distress—the identification of patients with ADHF remains challenging.²

Besides history, physical examination, and blood tests, the 12-lead electrocardiogram (ECG) plays a key role in the workup of patients with cardiorespiratory symptoms and is usually obtained within minutes in the ED. Its value in acute heart failure has, however, been limited predominantly to the identification of potentially precipitating causes of ADHF such as arrhythmias or myocardial infarction. Few studies evaluated its utility beyond this scope and, among others, identified prolongation of QRS and QTc duration to be associated with an increased risk for adverse events.³

A readily available ECG parameter that has recently gained attention is the QRS-T angle. It is the angle between the axis of the QRS complex and the axis of the T-wave and represents a measure of cardiac depolarization–repolarization heterogeneity. It has recently been shown to improve the diagnostic accuracy in patients with suspected non-ST-elevation myocardial infarction, and large QRS-T angles have been associated with increased risk for ventricular arrhythmias, hospitalizations, and mortality in various populations.^{4–14}

The utility of the QRS-T angle in patients with suspected ADHF has not yet been assessed. The aim of this prospective multicentre study was therefore to evaluate the diagnostic and prognostic values of the QRS-T angle in patients presenting to the ED with symptoms suggestive of ADHF.

Methods

Study design and population

Unselected patients presenting to the Emergency Departments of the University Hospital of Basel or the University Hospital of Zürich, Switzerland, with the leading symptom of acute dyspnoea were prospectively enrolled between May 2001 and December 2015. Exclusion criteria were age below 18 years, an obvious traumatic cause of dyspnoea, cardiogenic shock, and terminal kidney failure requiring dialysis. The study was approved by the local ethics committees and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Routine clinical assessment

In all patients, routine clinical assessment including demographic factors, medical history, physical examination, 12-lead ECG, continuous ECG monitoring, pulse oximetry, standard blood tests, and chest radiography were performed. Standard blood tests included high-sensitivity troponin T (hs-TnT; Roche Diagnostics, Rotkreuz, Switzerland) and the N-terminal pro-B-type natriuretic peptide (NT-proBNP; Roche Diagnostics, Rotkreuz, Switzerland). Additional diagnostic tests and therapeutic actions were left to the discretion of the attending physician.

Adjudication of final diagnoses

The final diagnosis was adjudicated by a single internal medicine specialist up to 2002 and by two independent cardiologists thereafter in the core laboratories of the University Hospitals Basel and Zürich after review of all available medical records, including the baseline evaluation, results of subsequent laboratory and radiologic tests, ECGs, echocardiographies, response to therapy, and autopsy data if available, from the time of ED presentation up to 90 days of follow-up. In case of disagreement, a third cardiologist was consulted, and consensus was found upon joined review of available material. The diagnosis of ADHF was based on the applicable guidelines of the European Society of Cardiology for each period.^{15–18}

Digital electrocardiogram recording, automated calculation of the QRS-T angle, and automated analysis of the QRS-T confounder type

Ten-second 12-lead ECGs were acquired as part of the routine clinical assessment in the ED using an AT-110 ECG device (Schiller AG, Baar, Switzerland) or a Page Writer TC30 ECG device (Philips Healthcare, Andover, MA, USA). The digital ECG raw data were recorded using a sampling rate of 500 Hz, a resolution of 5 μ V/bit, and a diagnostic signal bandwidth of 0.05 to 150 Hz (fulfilling the requirements by current international ECG device standards).

The ETM V01.12.09.00 ECG analysis program (Schiller AG, Baar, Switzerland) was used to automatically measure ECG features, including amplitudes, depolarization and repolarization timings, and frontal plane QRS and T-wave axis (summation vector of frontal plane QRS, respectively, T-wave). To minimize random noise and to improve the signal to noise ratio, median beats were used for all quantitative measures as described by Kligfield *et al.*¹⁹ To construct the median heart-beat, a high-pass filter was applied to the ECG signal to remove baseline wandering. A QRS detector determined the position of all heartbeats in the 10 s 12-lead ECGs. Beats were

then classified by cross-correlation of the QRS complexes. The QRS class with the most QRS complexes and the shortest QRS duration was defined as the predominant normal heartbeat. Those predominant normal heartbeats were then temporally aligned by maximization of the cross-correlation of the QRS complexes. From the aligned heartbeats, which are time series, a robust median was calculated for each time point (sample) in the time series. The QRS-T angle was subsequently calculated as the absolute difference between the QRS and T-wave axis. If the difference exceeded 180° , the value was subtracted from 360° (Figure S1). Automated analysis of the ECG confounder types [intermediate: isolated right bundle branch block (RBBB) and left ventricular hypertrophy; remarkable: left bundle branch block, non-specific bundle branch block, left anterior fascicular block (LAFB), and RBBB + LAFB] was classified based on automated diagnostic statement codes (ETM V01.12.09.00, Schiller AG, Baar, Switzerland), QRS duration, and QRS axis as previously reported by Strauss *et al.*²⁰

Follow-up

Patients were contacted 1 and 2 years after hospital discharge by phone or in written form by trained researchers. In case of missing information, the national registry on mortality, the hospital's diagnosis registry, and the family physician's records were assessed.

Outcomes and statistical analysis

Data are presented as median [inter-quartile range (IQR)] in case of continuous variables and as numbers and percentages in case of categorical variables. Comparison between groups was performed using Pearson's χ^2 test, Mann–Whitney *U* test, and Kruskal–Wallis test as appropriate. The primary diagnostic endpoint was an adjudicated final diagnosis of ADHF. Pre-specified subgroup analyses for the diagnostic endpoint were planned in patients with advanced age (>75 years), atrial fibrillation (AF) at presentation, and renal failure [estimated glomerular filtration rate (eGFR) < 30 mL/min/ 1.73 m²]. Diagnostic accuracy was assessed by receiver operating characteristic (ROC) analysis with calculation of the area under the ROC curve (AUC) and comparison of ROC AUCs using the non-parametric method as recommended by DeLong *et al.*²¹ Additionally, univariable and multivariable binary logistic regression models were computed to quantify the association between selected baseline variables and the diagnosis of ADHF as odds ratios (ORs) with 95% confidence intervals (CIs). Variables were selected based on clinical importance and tested for their association with the diagnosis of ADHF in univariable analyses first. Parameters with a

P-value < 0.1 in univariate tests were entered into the multivariable model.

The primary prognostic endpoint was all-cause mortality during 2 years of follow-up. The secondary prognostic endpoint was all-cause re-hospitalizations during 2 years of follow-up. To evaluate time to event outcomes, we constructed Kaplan–Meier curves and used the log-rank test to assess statistical significance. Univariable and multivariable Cox proportional hazard analyses with calculation of hazard ratios (HRs) with 95% CI were performed to quantify 2 year mortality risk. As for logistic regression, we selected variables by clinical reasoning and entered those with a *P*-value < 0.1 in univariable analysis into the multivariable model. For all tests, a two-tailed *P*-value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS Statistics version 25 (IBM, Chicago, Illinois, USA) and STATA Statistical Software version 15.1 (StataCorp, College Station, Texas, USA).

Results

Baseline characteristics

A total of 3116 unselected patients presenting to the ED with the chief complaint of acute dyspnoea were enrolled between 2001 and 2015. After exclusion of patients without digital ECG records ($n = 1158$), with unclear final diagnoses ($n = 13$) or with an adjudicated final diagnosis of ST-elevation myocardial infarction or ventricular arrhythmia (where no further diagnostics are required, $n = 30$), 1915 patients were available for analysis (Figure S2).

Baseline characteristics are presented in Table 1. ADHF was the adjudicated final diagnosis in 60% of patients ($n = 1140$). Non-cardiac causes of dyspnoea were responsible for the remaining 40% ($n = 775$) and included asthma or chronic obstructive pulmonary disease (COPD) exacerbations, bacterial or viral infections, pulmonary embolisms, and other causes.

Levels of the QRS-T angle and QRS-T confounders

The median QRS-T angle in the overall population was 66° (IQR 25 – 139°). Levels of the QRS-T angle were associated with several baseline characteristics, as shown in Table 2. Patients with higher QRS-T angles were older, were more commonly male, and had a higher rate of co-morbidities such as arterial hypertension, coronary artery disease, or chronic kidney disease (CKD).

Presence and type of ECG confounders of cardiac depolarization and repolarization resulted in significant changes in the QRS-T angle. The ECG was free of confounders in 59% of patients. In those, the median QRS-T angle was 39°

Table 1 Baseline characteristics

Variable	All patients (<i>n</i> = 1915)	Acute decompensated heart failure (<i>n</i> = 1140)	Non-cardiac dyspnoea (<i>n</i> = 775)	<i>P</i> -value ^a
Age (years), median [IQR]	76 [64–83]	79 [70–85]	69 [56–78]	<0.001
Male sex, <i>n</i> (%)	1071 (56)	646 (43)	425 (45)	0.43
BMI (kg/m ²), median [IQR]	26 [23–30]	26 [23–30]	26 [22–30]	0.03
Current smoking, <i>n</i> (%)	396 (21)	196 (18)	200 (26)	<0.001
Co-morbidities, <i>n</i> (%)				
Art. hypertension	1340 (71)	893 (80)	447 (58)	<0.001
Dyslipidaemia	841 (45)	578 (51)	263 (34)	<0.001
Diabetes mellitus	454 (24)	323 (29)	131 (17)	<0.001
CAD	708 (37)	556 (50)	152 (20)	<0.001
Prior MI	391 (21)	314 (29)	77 (10)	<0.001
PM, ICD, or CRT	147 (8)	140 (12)	7 (1)	<0.001
Atrial fibrillation	547 (30)	472 (43)	75 (10)	<0.001
COPD	610 (32)	284 (25)	326 (42)	<0.001
CKD	606 (32)	502 (45)	103 (13)	<0.001
Dyspnoea, <i>n</i> (%)				<0.001
NYHA II	197 (10)	74 (6.5)	123 (16)	
NYHA III	832 (43)	522 (46)	310 (40)	
NYHA IV	805 (42)	496 (44)	309 (40)	
Vital signs, median [IQR]				
sBP (mmHg)	138 [122–156]	137 [20–156]	139 [125–156]	0.06
dBP (mmHg)	80 [68–91]	80 [68–93]	80 [69–90]	0.72
Heart rate (b.p.m.)	86 [72–101]	87 [71–105]	85 [73–99]	0.08
ECG findings, <i>n</i> (%) or median [IQR]				
Rhythm				
Sinus	1436 (75)	712 (62)	724 (93)	<0.001
Atrial fibrillation	479 (25)	428 (38)	51 (7)	<0.001
Ventricular pacing	72 (4)	65 (6)	7 (1)	<0.001
QRS duration (ms)	96 [86–118]	104 [90–132]	92 [84–100]	<0.001
QTc time (ms)	454 [430–481]	468 [444–494]	439 [420–458]	<0.001
QRS-T angle (°)	66 [25–139]	110 [46–156]	33 [15–67]	<0.001
QRS-T confounders				<0.001
None	1134 (59)	530 (47)	604 (78)	<0.001
Intermediate	416 (22)	298 (26)	118 (15)	<0.001
Remarkable	365 (19)	312 (27)	53 (6.8)	<0.001
Laboratory tests, median [IQR]				
Haemoglobin (g/L)	132 [117–145]	127 [113–141]	139 [136–150]	<0.001
CRP (mg/L)	12 [3.7–38]	11 [4.1–31]	13 [3.0–58]	0.07
eGFR (mL/min/m ²)	65 [42–86]	53 [35–74]	83 [62–99]	<0.001
NT-proBNP (pg/mL) ^b	2032 [354–6453]	5083 [2237–9921]	252 [83–750]	<0.001
hs-TnT (ng/mL) ^c	0.03 [0.01–0.05]	0.04 [0.02–0.07]	0.01 [0.01–0.03]	<0.001

Abbreviations: Art, arterial; BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker; sBP, systolic blood pressure.

^aFor comparison between acute decompensated heart failure and non-cardiac dyspnoea. Between-group comparisons were performed using Pearson's χ^2 test in case of nominal and Mann-Whitney *U* test in case of ordinal or continuous variables.

^bAvailable for 1848 patients.

^cAvailable for 1791 patients.

(IQR 17–88°). It increased to 99° (IQR 41–149°) in patients with intermediate ECG confounders (22% of patients overall) and to 154° (IQR 108–170°) in those with remarkable ECG confounders (19% of patients overall).

Diagnostic value of the QRS-T angle for the discrimination between acute decompensated heart failure and non-cardiac causes of dyspnoea

The QRS-T angle was significantly greater in patients with ADHF compared with patients with non-cardiac causes of

dyspnoea [110° (IQR 46–156°) vs. 33° (IQR 15–57°), $P < 0.001$, *Figure 1A*]. The diagnostic accuracy of the QRS-T angle at presentation for discrimination between ADHF or non-cardiac causes of dyspnoea as quantified by the AUC in the overall cohort was 0.75 (95% CI 0.73–0.77, $P < 0.001$). Choosing a cut-off value of 63° (based on Youden's index), 70% of patients were correctly classified (sensitivity 69%, specificity 73%, positive predictive value 79%, and negative predictive value 61%; *Table S1*).

QRS-T angles were significantly higher in patients with ADHF as compared with patients with non-cardiac causes of dyspnoea irrespective of the presence and type of QRS-T

Table 2 Patient characteristics stratified on QRS-T angle

Variable	QRS-T angle < 35° (n = 641)	QRS-T angle 35–114° (n = 635)	QRS-T angle > 114° (n = 639)	P-value
Age (years), median [IQR]	72 [59–82]	76 [64–83]	78 [69–84]	<0.001
Male sex, n (%)	321 (50)	360 (57)	390 (61)	<0.001
BMI (kg/m ²), median [IQR]	26 [22–30]	26 [23–30]	26 [23–29]	0.72
Current smoking, n (%)	142 (23)	129 (21)	124 (20)	0.46
Co-morbidities, n (%)				
Art. hypertension	413 (65)	442 (70)	485 (78)	<0.001
Dyslipidaemia	248 (39)	258 (42)	335 (55)	<0.001
Diabetes mellitus	120 (19)	153 (24)	181 (29)	<0.001
CAD	171 (27)	207 (33)	330 (53)	<0.001
Prior MI	83 (13)	118 (19)	190 (31)	<0.001
PM, ICD, or CRT	21 (3)	37 (6)	89 (14)	<0.001
Atrial fibrillation	113 (18)	183 (30)	251 (41)	<0.001
COPD	232 (36)	213 (34)	165 (26)	0.003
CKD	140 (22)	175 (28)	291 (47)	<0.001
Dyspnoea, n (%)				<0.001
NYHA II	84 (13)	77 (12)	36 (5.6)	
NYHA III	288 (45)	255 (40)	289 (45)	
NYHA IV	244 (38)	271 (43)	290 (45)	
Vital signs, median [IQR]				
sBP (mmHg)	138 [124–157]	140 [125–158]	133 [117–152]	<0.001
dBP (mmHg)	80 [68–91]	81 [68–93]	79 [67–91]	0.29
Heart rate (b.p.m.)	83 [70–97]	87.3 [74–103]	88.6 [73–106]	<0.001
ECG findings, n (%) or median [IQR]				
Rhythm				
Sinus	548 (86)	478 (75)	410 (64)	<0.001
Atrial fibrillation	93 (15)	157 (25)	229 (36)	<0.001
Ventricular pacing	8 (1)	13 (2)	51 (8)	<0.001
QRS duration (ms)	90 [84–98]	96.0 [86–110]	116.0 [96–144]	<0.001
QTc time (ms)	442 [423–465]	453.0 [431–473]	473.0 [446–501]	<0.001
QRS-T confounders, n (%)				
None	535 (84)	403 (64)	196 (31)	<0.001
Intermediate	88 (14)	156 (25)	172 (27)	<0.001
Remarkable	18 (2.8)	76 (12)	271 (42)	<0.001
Laboratory tests, median [IQR]				
Haemoglobin (g/L)	133 [119–146]	133 [120–146]	130 [115–142]	0.001
CRP (mg/L)	11 [3–47]	14 [4–42]	11 [4–30]	0.03
eGFR (mL/min/m ²)	75 [52–93]	65 [44–88]	52 [36–75]	<0.001
NT-proBNP (pg/mL) ^a	508 [118–2536]	1831 [312–5240]	5556 [2066–11 663]	<0.001
hs-TnT (ng/mL) ^b	0.02 [0.01, 0.04]	0.02 [0.01–0.05]	0.04 [0.02–0.07]	<0.001
Discharge diagnosis, n (%)				<0.001
ADHF	232 (36)	365 (58)	543 (85)	
Non-cardiac cause	409 (64)	270 (43)	96 (15)	

Abbreviations: ADHF, acute decompensated heart failure; Art, arterial; BMI, body mass index; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CRP, C-reactive protein; CRT, cardiac resynchronization therapy; dBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; hs-TnT, high-sensitivity troponin T; ICD, implantable cardioverter-defibrillator; MI, myocardial infarction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PM, pacemaker; sBP, systolic blood pressure.

Between-group comparisons were performed using Pearson's χ^2 test in case of nominal and Kruskal–Wallis test in case of ordinal or continuous variables.

^aAvailable for 1848 patients.

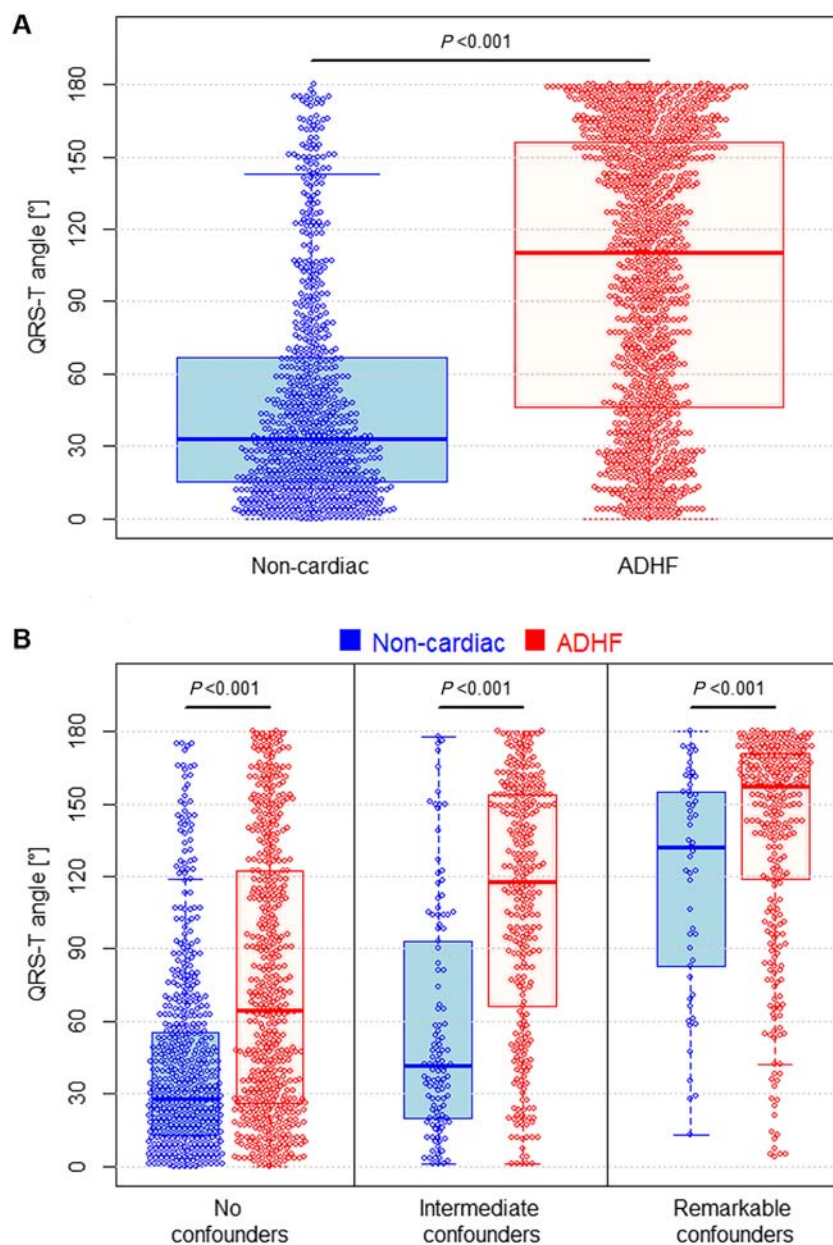
^bAvailable for 1791 patients.

confounders (Figure 1B, all $P < 0.001$). Accordingly, the AUC was not different for patients with no ECG confounders (AUC 0.69, 95% CI 0.65–0.72), intermediate ECG confounders (AUC 0.76, 95% CI 0.71–0.81), and remarkable ECG confounders (AUC 0.65, 95% CI 0.58–0.72).

The AUC of the QRS-T angle for discrimination between ADHF and non-cardiac dyspnoea remained similarly high in subgroups of patients known to be diagnostically challenging, including patients older than 75 years [0.71 (95% CI 0.67–0.74)], with renal failure [0.79 (95% CI 0.71–0.87)], and with

AF at presentation [0.68 (95% CI 0.60–0.76)]. For comparison, the diagnostic accuracy of hs-TnT decreased from an AUC of 0.78 (95% CI 0.76–0.80) in the overall population and 0.68 (95% CI 0.65–0.72) in patients > 75 years, to 0.60 (95% CI 0.50–0.70) in patients with renal failure, and to 0.52 (95% CI 0.43–0.61) in patients presenting with AF. The AUCs of the QRS-T angle and hs-TnT were statistically not different in the overall population and in patients > 75 years, while in patients with renal failure and AF, the QRS-T angle was superior to hs-TnT ($P < 0.001$ and $P = 0.002$). Compared with

Figure 1 QRS-T angle in patients with acute decompensated heart failure versus other causes of acute dyspnoea. QRS-T angle in patients with ADHF (displayed in red) and non-cardiac causes of acute dyspnoea (displayed in blue) in the overall population (A), and stratified according to the presence of no, intermediate (RBBB, LVH), and remarkable (LAFB, RBBB+LAFB, LBBB, and NBBB) ECG confounders (B). Mann–Whitney *U* test used for comparison. Abbreviations: ADHF, acute decompensated heart failure; RBBB, right bundle branch block; LVH, left ventricular hypertrophy; LAFB, left anterior fascicular block; LBBB, left bundle branch block; NBBB, non-specific bundle branch block.



those of NT-proBNP (the biomarker assisting in gold-standard adjudication in this study), the AUCs of both the QRS-T angle and hs-TnT were lower in the overall population as well as in all subgroups (Table S1). Cut-offs with respective sensitivities, specificities, and positive and negative predictive values are summarized in Table S2.

Without adjustment for other factors, the odds for ADHF increased by 42% (OR 1.42, 95% CI 1.37–1.48, $P < 0.001$)

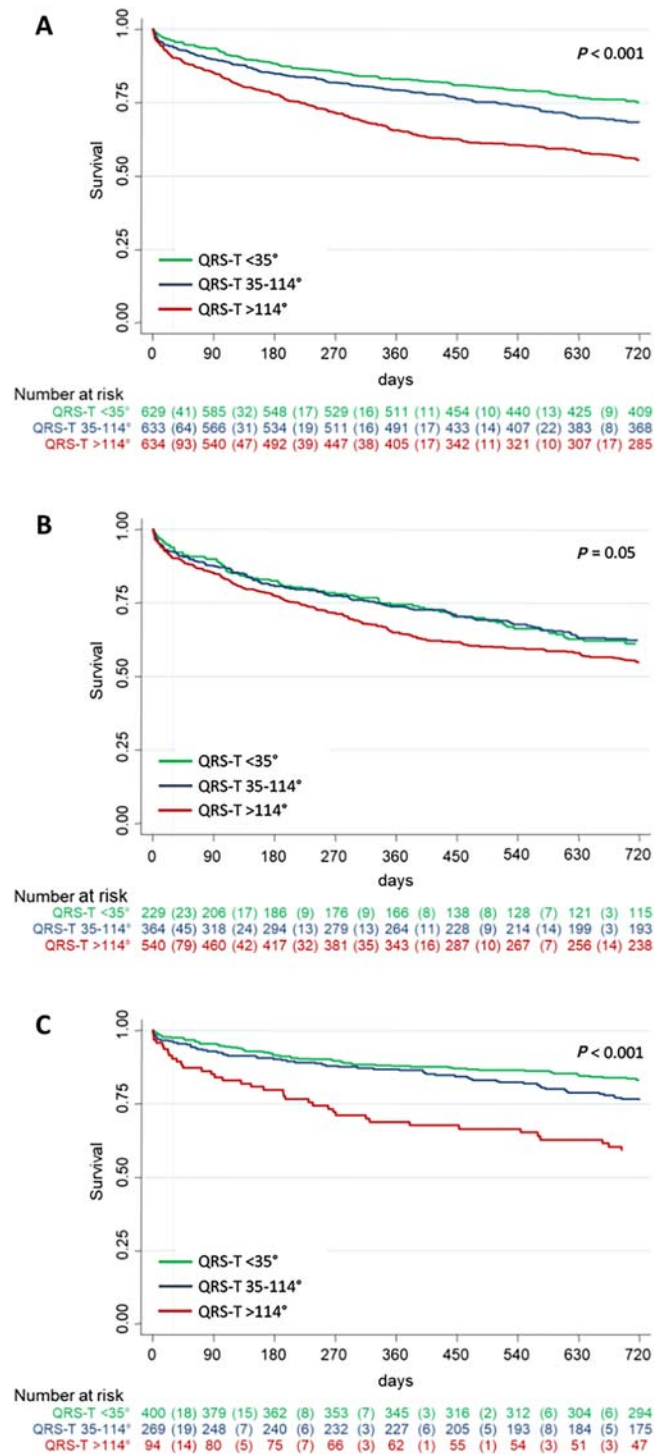
for every 20° increase of the QRS-T angle (Table S3). In a multivariable model including patient age, body mass index (BMI), medical history (arterial hypertension, dyslipidaemia, coronary artery disease, AF, and COPD), eGFR, NT-proBNP, hs-TnT, and QRS and QTc duration, the QRS-T angle remained predictive for ADHF with an OR of 1.17 (95% CI 1.10–1.24) per 20° increase ($P < 0.001$; Table S3).

Prognostic value of the QRS-T angle

A total of 793 patients (42%) died during a median follow-up time of 28 months (IQR 27–39). Those who died had

significantly higher QRS-T angles than had survivors [96° (IQR 35–153°) vs. 51° (IQR 20–121°), $P < 0.001$]. Survival according to QRS-T angle tertiles was 96%, 94%, and 90% after 30 days ($P < 0.001$) and 76%, 69%, and 57% after 2 years

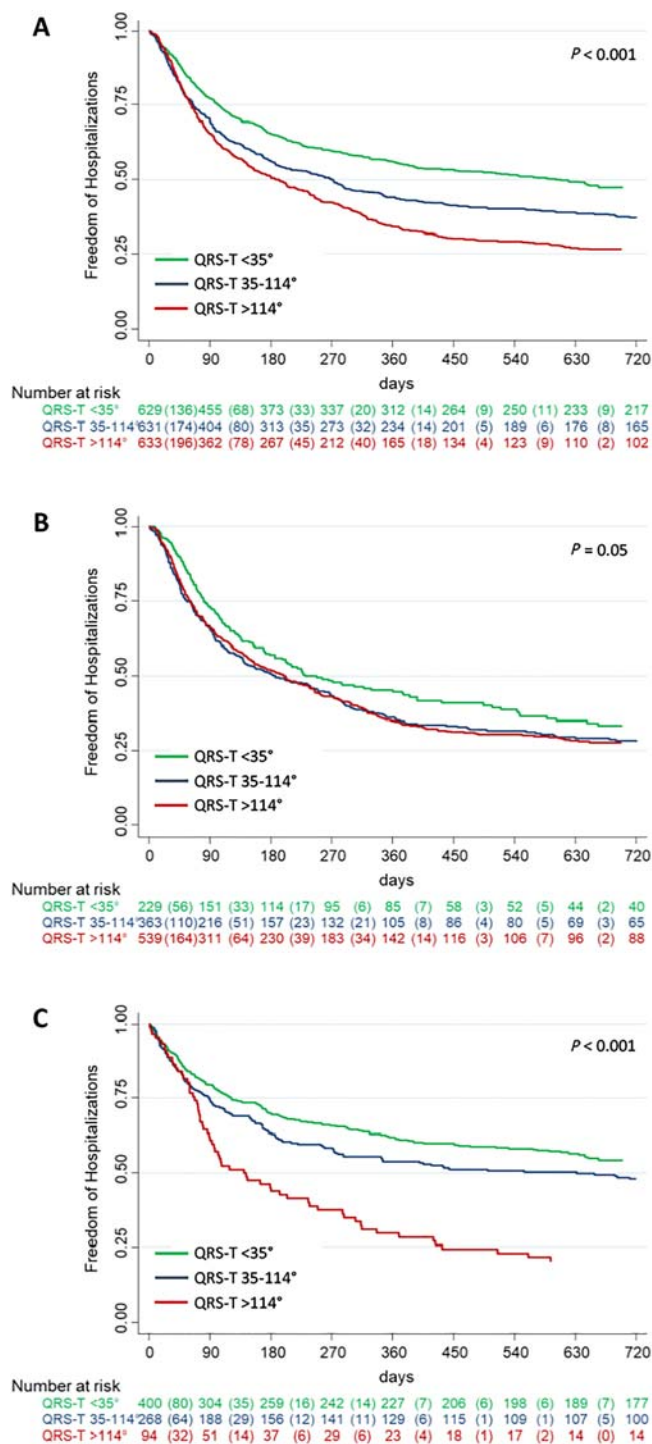
Figure 2 Prognostic value of the QRS-T angle with respect to all-cause mortality. Kaplan–Meier survival estimates according to QRS-T angle tertiles in the overall population (A), in patients with acute decompensated heart failure (B), and in patients with non-cardiac cause of acute dyspnoea (C).



($P < 0.001$, Figure 2A). The QRS-T angle was associated with survival both in patients with ADHF (Figure 2B) and in patients with non-cardiac causes of dyspnoea (Figure 2C).

Similarly, the QRS-T angle predicted freedom from re-hospitalizations during 2 years of follow-up in the overall cohort (Figure 3A), as well as in the subgroups of patients

Figure 3 Prognostic value of the QRS-T angle with regard to all-cause re-hospitalizations. Cumulative re-hospitalization risk according to QRS-T angle tertiles in the overall population (A), in patients with acute decompensated heart failure (B), and in patients with non-cardiac cause of acute dyspnoea (C).



with ADHF (Figure 3B) and non-cardiac causes of dyspnoea (Figure 3C).

In univariable Cox proportional hazard analysis, the QRS-T angle predicted mortality after 2 years in the whole population with an HR of 1.12 (95% CI 1.09–1.14, $P < 0.001$) for every 20° increment (Table 3). It remained predictive of 2 year mortality even after adjustment for age, sex, BMI, co-morbidities (arterial hypertension, dyslipidaemia, coronary artery disease, AF, and COPD), systolic blood pressure, eGFR, NT-proBNP, hs-TnT, and QRS and QTc duration (HR 1.04, 95% CI 1.01–1.07, $P = 0.02$; Table 3). Similar results were observed also for re-hospitalizations (HR 1.42, 95% CI 1.37–1.48, $P < 0.001$ in univariable analysis, HR 1.17, 95% CI 1.10–1.24, $P < 0.001$ in multivariable analysis adjusting for the factors mentioned above, per 20° increase of the QRS-T angle), as shown in Table S3.

Discussion

This large multicentre observational cohort study assessed the diagnostic and prognostic values of the QRS-T angle, a simple and readily available, observer-independent ECG marker quantifying depolarization–repolarization heterogeneity, in patients admitted to the ED with the chief complaint of acute dyspnoea suggestive of ADHF. We observed five major findings:

First, the QRS-T angle was significantly higher—nearly three times as high—in patients with ADHF compared with non-cardiac causes of acute dyspnoea. After adjustment for several clinical, laboratory, and ECG variables, the odds for ADHF increased by 17% for every 20° increase in the QRS-T angle. Second, the diagnostic accuracy of the QRS-T angle to detect patients with ADHF was similar to that of hs-TnT and, in contrast to the latter, remained high in subgroups of patients known to be diagnostically challenging, such as those with renal failure and AF. Third, patients with higher QRS-T angles had a higher risk for re-hospitalizations and mortality. During 2 years of follow-up, nearly 50% of patients in the highest QRS-T angle tertile died, which was almost twice as many as those in the lowest tertile. Fourth, even after adjustment for multiple baseline characteristics, including but not limited to age, co-morbidities, and importantly NT-proBNP, the QRS-T angle remained independently predictive of 2 year mortality with a risk increase of 4% for every 20°. Fifth, the QRS-T angle predicted re-hospitalizations and mortality both in patients with ADHF as well as those with non-cardiac causes of dyspnoea independently, highlighting its prognostic value irrespective from the underlying condition.

These findings have several clinical implications. Despite advances in diagnostic abilities, rapid and reliable identification of patients with acute heart failure in the emergency setting remains challenging. Imaging modalities provide ample information, yet their limited availability and dependence on operator skills restrict their applicability to centres with

Table 3 Univariable and multivariable predictors for long-term mortality in patients presenting to the emergency department with acute dyspnoea

	Univariable				Multivariable			
	HR	LCI	UCI	P-value	HR	LCI	UCI	P-value
Age (per year)	1.05	1.04	1.06	<0.001	1.04	1.03	1.05	<0.001
Male sex	0.87	0.76	1.01	0.08	0.76	0.65	0.90	0.001
BMI	0.95	0.94	0.96	<0.001	0.96	0.94	0.97	<0.001
Medical history								
Art. hypertension	1.63	1.37	1.94	<0.001	0.97	0.79	1.20	0.80
Dyslipidaemia	1.24	1.07	1.43	0.004	0.93	0.77	1.11	0.42
CAD	1.60	1.39	1.85	<0.001	1.05	0.87	1.25	0.63
Atrial fibrillation	1.60	1.38	1.86	<0.001	0.99	0.84	1.18	0.98
COPD	1.21	1.04	1.40	0.01	1.37	1.16	1.61	<0.001
Diabetes mellitus	1.17	0.99	1.37	0.05	1.35	1.12	1.63	0.002
Vital signs								
Heart rate (b.p.m.)	1.00	1.00	1.00	0.74	—	—	—	—
sBP (per 10 mmHg)	0.92	0.90	0.95	<0.001	0.94	0.91	0.97	<0.001
Laboratory tests								
eGFR > 60 mL/min/m ²	0.40	0.35	0.47	<0.001	0.64	0.54	0.77	<0.001
NT-proBNP (per 100 pg/mL)	1.001	1.001	1.001	<0.001	1.000	1.000	1.001	<0.001
hs-TnT (per ng/mL)	1.61	1.28	2.03	<0.001	1.18	0.87	1.56	0.29
ECG parameters								
QRS-T angle (per 20°)	1.12	1.09	1.14	<0.001	1.04	1.01	1.07	0.02
QRS duration (per 10 ms)	1.07	1.05	1.10	<0.001	0.99	0.99	1.00	0.64
QTc duration (per 10 ms)	1.05	1.03	1.07	<0.001	1.00	0.99	1.10	0.18

Abbreviations: Art, arterial; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; hs-TnT, high-sensitivity troponin T; LCI, lower confidence interval; NT-proBNP, N-terminal pro-B-type natriuretic peptide; sBP, systolic blood pressure; UCI, upper confidence interval.

on-site expertise. Blood tests are invaluable in the assessment of suspected ADHF. However, the time it takes until results are obtained may delay diagnosis and treatment initiation, which has been associated with prolonged hospitalization durations and increased mortality.^{22,23} A 12-lead ECG is routinely obtained in any patient with potentially cardiac mediated symptoms and has the advantage of general availability and immediate interpretability. Its role in acute heart failure, however, has been primarily restricted to the identification of potentially precipitant causes for ADHF.^{15,24} So far, no single ECG parameter has been found to predict the probability of ADHF even though it is recognized that patients with heart failure often have abnormal ECGs.²⁴ Accordingly, the QRS-T angle reported in this study is the first readily available and easily interpretable ECG parameter that may aid in the diagnosis of patients with suspected ADHF. To put it in context, we compared its diagnostic value for a diagnosis of ADHF with that of hs-TnT, which has increasingly gained attention owing to its potential diagnostic and prognostic impact,^{25–27} as well as with that of NT-proBNP, which was used as the biochemical gold standard for the adjudicated final diagnosis of ADHF. Not surprisingly, both the QRS-T angle and hs-TnT had a lower diagnostic performance than NT-proBNP. On the other hand, the diagnostic accuracy of the QRS-T angle in the overall population was similar to that of hs-TnT and, in contrast to troponin, which lost its informative value in patients with renal failure and AF, remained high in these populations. Patients with co-morbidities are known to be diagnostic challenging; nevertheless, they present a substantial proportion of patients presenting to the ED with respiratory distress—in our study, ~30% of patients had a history of AF or CKD, which is comparable with other cohorts in this setting. Including the easily available QRS-T angle—together with any other available information—into the full picture may aid in the diagnostic process and enhance fast yet accurate triage and resource allocation in order to ensure optimal management of patients.

Triage and resource allocation are central in EDs, which are faced with ever-rising patient volumes with increasingly complex disease manifestations.²⁸ Proper triage relies on adequate risk stratification and can be improved by incorporation of prognostic markers.²⁹ A number of previous investigations examined the prognostic value of the QRS-T angle in various populations, including patients with arterial hypertension, diabetes, CKD, myocarditis, implanted cardiac devices, chronic heart failure, and suspected and confirmed myocardial ischaemia, as well as in the general population.^{4–14} Across the spectrum, greater QRS-T angles were associated with increased risk of adverse events, re-hospitalizations, and mortality. These findings were corroborated in our study, which was the first to evaluate the prognostic value of the QRS-T angle in patients with symptoms suggestive of ADHF. Also, in our population, larger QRS-T angles were predictive of re-hospitalizations and

mortality, even after adjustment for multiple clinically relevant variables. Other ECG parameters that have been previously implied in a greater risk of adverse events, including death, in patients with ADHF are the QRS and QTc duration.^{3,30} Also, in our cohort, both QRS and QTc duration were associated with mortality during follow-up in univariable analysis but lost their significance upon adjustment for other baseline variables. Thus, among the ECG parameters readily available to the caretaker, the QRS-T angle may provide the greatest prognostic information, as has been suggested also in earlier reports.¹³ A reason for this observation may lie in the fact that the QRS-T angle is likewise affected by abnormal depolarization as well as repolarization, which makes it more robust and less susceptible to noise than parameters measuring either of these factors alone. Moreover, the QRS-T angle is a measure of electrical heterogeneity, which can occur at various stages in cardiac disease and is known to predispose for potentially lethal arrhythmias.

The findings of this study have to be interpreted in consideration of following limitations: First, patients with terminal renal failure requiring dialysis were excluded, wherefore the findings do not apply to this population. Second, the effect estimates of our multivariable analyses may be considered small. However, as the QRS-T angle is by no means meant to replace other parameters but shall rather be seen in conjuncture with them, also small contributions may sum up to a common whole and should therefore not be neglected—especially when they are free of additional effort and cost. Third, we calculated only the frontal QRS-T angle, while some authors have suggested that the spatial QRS-T angle may have higher diagnostic and prognostic accuracy.³¹ Fourth, we did not discriminate between newly diagnosed acute heart failure and decompensation of previously known chronic heart failure. Further investigations are needed to examine possible differences between these populations. Fifth, no detailed information was available on pacing modes in patients with cardiac devices. We were able to report the amount of patients with ventricular pacing but lack the data on atrial pacing. However, from a pathophysiological point of view, we do not think that atrial pacing should have had a relevant impact on the QRS-T angle. And finally, the analyses are based on QRS-T angles derived at a single point in time (i.e. at ED admission). While previous studies suggested that the QRS-T angle was relatively stable over time, it is possible that it may be acutely affected in the setting of decompensated heart failure.^{4,9} In the context of our current study, only admission ECGs were recorded. This precludes us from analysing the QRS-T angle at discharge of the index hospitalization, and accordingly of the temporal QRS-T angle variability. The topic however should be addressed in future studies and could even find a potential value of the QRS-T angle as an indicator of treatment response in patients with ADHF.

Conclusions

The QRS-T angle, a quickly obtainable and readily interpretable ECG parameter, may aid in the diagnosis of patients with suspected ADHF and independently predicts mortality during 2 years of follow-up. Being usually available within minutes after patients contact, it can assist in the early management and decision process until results of more advanced tests become available.

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Conflict of Interest

T.B. has received research grants from the Swiss National Science Foundation (PASMP3-134362), the Department of Internal Medicine, University Hospital Basel, Abbott, and Roche as well as speaker honoraria from Roche. C.M. has received research grants from the Swiss National Science Foundation, the Swiss Heart Foundation, the European Union, the Cardiovascular Research Foundation Basel, the KTI, the University of Basel, Abbott, Alere, AstraZeneca, Beckman Coulter, BG Medicine, Biomerieux, BRAHMS, Critical Diagnostics, Roche, Siemens, Singulex, Sphingotec, and 8sense as well as speaker/consulting honoraria from Abbott, Alere, AstraZeneca, Biomerieux, BMS, Boehringer Ingelheim, BRAHMS, Cardiorientis, Eli Lilly, Novartis, Roche, Sanofi, Siemens, and Singulex. T.R. has received research grants from the Goldschmidt-Jacobson Foundation, the Swiss National Science Foundation, the Swiss Heart Foundation, the

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Calculation of the QRS-T Angle.

Figure S2. Patient flow chart.

Table S1. Diagnostic accuracy of the QRS-T angle to discriminate between acute decompensated heart failure and non-cardiac causes of dyspnea compared to hs-TnT and the gold-standard NT-proBNP.

Table S2. Cut-off QRS-T angles to discriminate between acute decompensated heart failure and non-cardiac causes of dyspnea.

Table S3. Prediction of acute decompensated heart failure versus non-cardiac cause of dyspnea by clinically available information at emergency department presentation: univariable and multivariable logistic regression.

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